Allogeneic stem cell transplantation in acute myeloid leukemia

Natasha Ali,[1] Salman Naseem Adil,[1] Mohammad Usman Shaikh,[1] Nehal Masood[2]

[1]Department of Pathology and Microbiology; [2]Department of Medicine, The Aga Khan University Hospital, Karachi, Pakistan

Abstract

We report a case series of 12 patients with acute myeloid leukemia who underwent allogeneic stem cell transplant with a matched related donor. Male to female ratio was 1:1. The main complication post-transplant was graft-*versus*-host disease (n=7 patients). Transplant-related mortality involved one patient; cause of death was multi-organ failure. After a median follow up of 36.0±11.3 months, overall survival was 16%.

Introduction

Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow. This, together with the arrest of these cells, may result in hematopoietic insufficiency, such as granulocytopenia, thrombocytopenia or anemia.[1] Since there is no cancer registry in Pakistan, a study carried out at our center in 2002 reported 74 adult patients with acute myeloid leukemia during an 8-year study period.[2] Most younger patients with acute myeloid leukemia achieve complete remission with induction and consolidation chemotherapy regimens. However, these remissions are not sustainable even for patients who achieve complete remission 1 (CR1). The invariable risk of relapse requires consolidation with allogeneic stem cell transplant.[3]

In developing countries, non-malignant diseases such as thalassemia major and aplastic anemia account for the largest number of transplant procedures;[4] this is in complete contrast to the situation in developed countries. Here in Pakistan, treatment of AML is managed on an individual basis, since the cost of standard uncomplicated transplant ranges from $25,000-$30,000. Most of the transplants performed are privately funded, but philanthropists generally prefer to invest in pathologies that have a better overall survival. This also means that patients come to the attention of the physician late in their disease course.

The European Group for Blood and Marrow Transplantation 2004 survey reported acute myeloid leukemia to be the most common indication for allogeneic hematopoietic stem cell transplant.[5] The procedure offers a double benefit as the preparative regimen in myeloablative doses eradicates the leukemic cells and this is followed by the post-transplant graft-versus-leukaemia effect.

A number of retrospective and prospective studies have identified risk factors that play a role in determining post-transplant survival of patients with AML. The most important determinants of standard, intermediate and high-risk patient populations include gender, presenting white blood cell counts, and impact of cytogenetics.[6]

From 1984 till 2001, the Bordeaux Grenoble Marseille Toulouse intergroup followed a proactive strategy of performing early allogeneic stem cell transplant as part of consolidation in patients under the age of 45 years who had an HLA (human leukocyte antigen) identical sibling donor.[7] For patients without an HLA matched donor, further chemotherapy courses were given and these changed over the years on the basis of the experience gained from different studies. The results showed that allogeneic stem cell transplant (alloSCT) provided a survival advantage for an intermediate risk group. AlloSCT performed early in the disease course was not the optimal treatment for high-risk patients. Neither did it offer any advantage over intensive chemotherapy to low-risk patients. We report our experience of 12 patients with acute myeloid leukemia (relapsed and CR1) who underwent allogeneic stem cell transplant over a 7-year period. These results show the survival of patients from a developing country where stem cell transplant is an expensive approach that is beyond the financial means of most of the population.

Materials and Methods

This study ran from April 2004 till June 2012 and included patients with acute myeloid leukemia eligible for bone marrow transplant. Other inclusion criteria were: age up to 60 years, diagnosis of AML based on the French American British classification excluding acute promyelocytic leukemia, no history of myelodysplasia or previous cytotoxic therapy/radiation, and absence of concomitant disease.

Patients received induction chemotherapy with daunorubicin 45 mg/m^2 intravenously on Days 1-3 and cytarabine 100 mg/m^2 infusion on Days 1-7. Consolidation was given with high-dose cytarabine at a dose of 3 gm/m^2 administered by a 2-h infusion every 12 h on Days 1, 3 and 5. The most frequently used salvage chemotherapy regimen included idarubicin, fludarabine, cytarabine and G-CSF. Patients under the age of 60 years with an HLA matched sibling donor were then admitted to the bone marrow transplant unit.

After a baseline pre-transplant workup of the donor and patient, peripheral blood stem cells were collected using a COBE spectra cell separator. All donors received granulocyte colony-stimulating factor at a dose of 10 μg/kg/day.

The two conditioning regimens used for patients undergoing stem cell transplant were: i) busulfan 4 mg/kg/day for four days along with cyclophosphamide 60 mg/kg/day for two days; ii) cyclophosphamide 60 mg/kg/day for two days along with fractionated total body irradiation at a dose of 1.5 Gy twice daily for four days.

Standard prophylaxis was provided with ciprofloxacin (500 mg twice daily or 20-30 mg/kg/two divided doses), fluconazole (200 mg once daily or 6 mg/kg/day) and valaciclovir (500 mg twice daily or 10 mg/kg/twice daily); this was started on Day 5 in all patients. All patients were given a neutropenic diet and admitted to a protective isolation environment equipped with a high-efficiency particulate air filter, positive pressure and laminar airflow ventilation.

Graft-*versus*-host disease (GVHD) prophylaxis was given with cyclosporine starting at Day -1 (2.5 mg/kg q12-hourly) with regular monitoring of drug levels, methotrexate administered on Day +1 (15 mg/m^2), Day +3 (10 mg/m^2) and Day +6 (10 mg/m^2), and irra-

Correspondence: Natasha Ali, Department of Pathology and Microbiology, The Aga Khan University Hospital, P.O Box 3500. Stadium Road, Karachi, 74800, Pakistan.
Tel. +92.21.34861306 - Fax: +92.21.4934294.
E-mail: natasha.ali@aku.edu

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diated blood products.

The main patients' characteristics were statistically analyzed. Survival probabilities were estimated using the Kaplan-Meier method. Statistical analysis was performed using SPSS software version 19 (Chicago, IL, USA).

Table 1. Laboratory parameters of 12 patients with acute myeloid leukemia.

Parameters	Mean±standard deviation (range)
Hemoglobin (g/dL)	9.6±1.9 (7.8-12.8)
White blood cell count ($\times 10^9$)	127.7±118 (1.8-292)
Platelets ($\times 10^9$)	32±11 (19-45)

Results

From April 2004 till June 2012, 12 patients with acute myeloid leukemia received allogeneic stem cell transplant procedure. Male to female ratio was 1:1. Ten patients showed no cytogenetic abnormalities. One patient had Philadelphia positive acute myeloid leukemia while one had multiple abnormalities (Monosomy 8 and t11q; 23). Laboratory parameters of these patients are listed in Table 1.

Two patients received gender mismatched transplant while 3 had ABO blood group mismatched donors. All patients and donors were cytomegalovirus positive. Conditioning with busulfan and cyclophosphamide was given in 10 patients while the rest received total body irradiation based therapy. Median age was 26.5±11.5 years (range 9-50 years). One patient was under 15 years of age, while all the other patients were adults. Mean mononuclear cell count was 5.6×10^8/kg (range 3.5-8.3×10^8/kg). Stem cell source was peripheral blood progenitor cells for all patients. Engraftment was achieved in all except one patient. Median time to engraftment (absolute neutrophil count over 0.5×10^9/L for three consecutive days) was 15.5±4.5 days (range 10-26.3 days)

Post-transplant complications mainly included GVHD. Grade II acute GVHD was observed in 4 patients; chronic limited GVHD was seen in one patient and extensive GVHD in 2 patients, respectively. Biopsies were performed in n=4 patients for histopathological confirmation. Eight patients developed febrile neutropenia; of these, 2 had blood culture positive for staphylococcus species and enterococcus.

Transplant-related mortality involved one patient; cause of death was multi-organ failure. After a median follow up of 36.0±11.3 months, overall survival is 16%. Causes of death include transplant-related mortality (n=1), relapse of disease (n=7), fulminant hepatic failure (n=1), and acute GVHD (n=1).

Discussion

Over the last decade, two important observations have been made with regard to treatment of acute myeloid leukemia: i) sustainable remission rates can be obtained with a combination of chemotherapy and allogeneic stem cell transplant; ii) cytogenetic abnormalities have been seen to be the most important predictor of outcome. [8,9]

Here we have reported the outcome of 12 patients with AML who underwent allogeneic stem cell transplant. Due to the small size, firm conclusions cannot be made from this study.

There was no gender predilection observed although previous studies had reported an increased frequency in males. A study carried out in 2005 by Appelbaum *et al.*[10] in 968 patients showed no change in gender ratio with age. AML is primarily seen in adults and, although in this study we stratified patients according to age for transplant eligibility, the overall median age for AML in this region is relatively low compared to that reported in the international literature. The median age in this study was 26.5 years; this is in line with a previous study carried out in our center in 2005. Similarly, another center in Pakistan has reported even lower age values, *i.e.* 21 years, when the authors evaluated the treatment outcome of *de novo* AML.[11] Data reported in two studies from developed countries now show a median age of 52 and 67 years, respectively.[12,13] The reason for this difference is difficult to ascertain; however, it may be a true ethnic or geographical variation as seen in the presentation of other diseases from our region.

Peripheral blood progenitor cells (PBSC) are now being used for almost all hematopoietic transplant procedures. These cells have higher numbers of CD34 and T lymphocytes.[14] PBSC were used in all our patients. As a result, 11 of 12 patients engrafted. The only patient with graft failure died from multi-organ failure secondary to sepsis.

Grade I acute GVHD is generally understood to be associated with an improved post-transplant outcome. Grades above this result in a worse overall survival since the beneficial effect of suppressing leukemia relapse is complicated by the morbidity and mortality associated with GVHD.[15] Four patients in our study developed grade II acute GVHD. However, the cause of death in all these patients was disease relapse rather than the GVHD itself. In our group of patients, 3 underwent transplant procedure in CR1 (increased white blood cell counts, n=2; Philadelphia positive AML, n=1) whereas the remaining patients were in CR2. Small retrospective studies (less than 100 patients) have been reported for patients with AML not in remission undergoing stem cell transplant procedure. These studies have reported long-term survival rates of 20-30%.[16] In 2000, Michallet *et al.*[17] reported outcome of 379 patients. Of these, 230 received transplants with active disease. As expected, patients who underwent re-induction therapy first and achieved a complete remission did significantly better, with an overall survival of 32%. In 2010, the Center for International Blood and Bone Marrow Transplant Research reported the largest and most complete analysis of outcome of AML patients undergoing stem cell transplant.[18] The study included more than 2000 patients and overall survival at three years was 19%. In our series, overall survival was 16%. Although our subset is small, the results are still comparable with the overall survival of AML in patients of developed countries.

Conclusions

Acute myeloid leukemia is not the most common indication for stem cell transplant. Median patient age at presentation in our study is relatively low compared to developed countries. There was no gender preference observed in our study. In Pakistan, the cost of stem cell transplant procedures is beyond the means of most of the population, and this means that they come to the attention of physicians late in the disease course. In spite of this, overall survival is still comparable to that reported in the international literature.

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